Asia Pac Allergy. 2022 Jan;12(1):e6
https://doi.org/10.5415/apallergy.2022.12.e6
pISSN 2233-8276·eISSN 2233-8268

Asia Pacific allergy

Original Article

Allergen-specific immunotherapy practices and course of coronavirus disease 2019 (COVID-19) in patients during COVID-19

Merve Erkoç [1], Betül Özdel Öztürk [1], Dilşad Mungan [1], Derya Öztuna [2], Sevim Bavbek [1], Yavuz Selim Demirel [1], Ömür Aydın [1], and Betül Ayşe Sin [1,*]

[1]Division of Immunology and Allergy, Department of Chest Diseases, School of Medicine, Ankara University, Ankara, Turkey
[2]Department of Biostatistics, School of Medicine, Ankara University, Ankara, Turkey

Received: Nov 9, 2021
Accepted: Jan 18, 2022
Published online: Jan 24, 2022

***Correspondence to**
Betül Ayşe Sin
Division of Immunology and Allergy, Department of Chest Diseases, Ankara University School of Medicine, Dikimevi-Ankara 06100, Turkey.
Tel: +90-312-595-6553
Fax: +90-312-595-7310
Email: betulasin@gmail.com

ORCID iDs
Merve Erkoç
https://orcid.org/0000-0001-8147-3181
Betül Özdel Öztürk
https://orcid.org/0000-0001-8653-3497
Dilşad Mungan
https://orcid.org/0000-0001-8806-2764
Derya Öztuna
https://orcid.org/0000-0001-6266-3035
Sevim Bavbek
https://orcid.org/0000-0002-7884-0830
Yavuz Selim Demirel
https://orcid.org/0000-0002-1386-3353
Ömür Aydın
https://orcid.org/0000-0002-3670-1728

ABSTRACT

Background: Allergen-specific immunotherapy (AIT) is accepted as the only disease-modifying therapy for IgE-mediated allergic airway diseases and hymenoptera venom allergy. AIT requires repeated contact between patient and physician or nurse in the hospital. Because it is a long-term treatment, compliance is essential issue to obtain maximal efficacy. Coronavirus disease 2019 (COVID-19) pandemic reshaped doctor-patient interaction and pattern of hospital admissions.
Objective: We aimed to determine the possible changes in the administration of AIT and associated factors, in addition to the characteristics of patients diagnosed with COVID-19 infection.
Methods: Adult patients who underwent AIT for hymenoptera venom allergy, allergic rhinitis or allergic asthma between 11 March 2020 and 31 January 2021 were included in our retrospective study. Perennial and preseasonal AIT practices were evaluated. We identified patients with COVID-19 infection among the ones who received AIT.
Results: The mean age of 215 patients was 37.8±11.9 years and 52.1% of the patients were female. In our study, 35.4% of perennial AIT patients did not continue treatment after the COVID-19 pandemic, and the cause was patient-related in 66.7% of the cases. Compliance was 70.7% in patients receiving perennial AIT. The highest compliance rate for AIT was for venom allergy (86.5%). Thirty-four patients (15.8%) were diagnosed with COVID-19 infection. No mortality due to COVID-19 infection was observed in those who underwent AIT.
Conclusion: COVID-19 pandemic has reduced compliance to AIT. Compliance was higher in venom immunotherapy than in aeroallergens. Severe COVID-19 infection and COVID-19 related death were not observed in patients receiving AIT.

Keywords: Allergen-specific immunotherapy; Subcutaneous immunotherapy; Venom immunotherapy; Coronavirus disease 2019; Compliance; Adults

INTRODUCTION

Allergen-specific immunotherapy (AIT) is an effective and immune modulating treatment providing tolerance to allergens for allergic airway diseases and hymenoptera venom anaphylaxis

Betül Ayşe Sin
https://orcid.org/0000-0002-8896-9101

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Betül Ayşe Sin, Merve Erkoç. Formal analysis: Derya Öztuna, Merve Erkoç, Betül Özdel Öztürk. Investigation: Merve Erkoç, Betül Ayşe Sin. Methodology: Merve Erkoç, Betül Özdel Öztürk, Betül Ayşe Sin. Project administration: Betül Ayşe Sin, Merve Erkoç, Dilşad Mungan. Writing - original draft: Merve Erkoç, Betül Ayşe Sin. Writing - review & editing: Merve Erkoç, Betül Ayşe Sin, Dilşad Mungan, Sevim Bavbek, Yavuz Selim Demirel, Ömür Aydın.

[1]. In AIT, the allergen can be administered at regular intervals, as subcutaneous injections or sublingually liquid drops/fast-dissolving tablet forms. Depending on the duration of exposure to inhalant allergens, AIT can be arranged as pre-/coseasonal or perennial scheduals. A minimum of 3 years of treatment with AIT is recommended to achieve long-term clinical efficacy [2].

Coronavirus disease 2019 (COVID-19) is known as a disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a new type of coronavirus. It was first detected in December 2019, with cases in China. The World Health Organization (WHO) declared a global pandemic on March 11, 2020 and then, the first case was announced by the Ministry of Health in Turkey. In addition, people of all ages can be infected with SARS-CoV-2 and it has been stated that the elderly and those with underlying comorbid chronic diseases, other medical conditions are at higher risk of contracting severe COVID-19 during the time frame of the pandemic. It has also been recommended by WHO that everyone should protect themselves from COVID-19 [3, 4]. SARS-CoV-2 is a highly contagious virus and general measures including hand hygiene, social distance, use of a face mask, cleaning of the facilities become important interventions in reducing spread of virus. Furthermore, the COVID-19 outbreak has challenged healthcare systems capacities, and safety for health care workers to minimize hospital visits for avoiding transmission of virus. Therefore pandemic situation reshaped doctor-patient interaction, favoring remote video or phone consultation in the allergic patients instead of face to face evaluation or regular visits [5].

AIT requires repeated contact between patient and physician or nurse over a longer period of time such as 3 to 5 years. Especially in subcutaneous immunotherapy (SCIT), injections are given weekly during up-dosing phase and every for 4 to 6 weeks during maintenance period of time. AIT guidelines mostly indicate that in patients with acute respiratory tract infection, treatment should be temporarily suspended until the infection is subside. According to the Allergic Rhinitis and its Impact on Asthma (ARIA)-European Academy of Allergy and Clinical Immunology (EAACI) position paper, same principal is also advised for patients diagnosed with COVID-19, those suspected of SARS-CoV-2 infection, or symptomatic subjects with positive contact to infected COVID-19 individuals. AIT should be interrupted until the patient has recovered. However, it is recommended not to discontinue SCIT during the COVID-19 pandemic, and it is stated that SCIT should be administered regularly, especially in potentially life-threatening allergies such as hymenoptera venom allergy. The possibility of extending injection intervals in the maintenance phase should be considered and may be useful [6].

During the COVID-19 pandemic, we aimed to evaluate whether there was any interruptions or drop-outs in the treatment practices and their reasons, the status of dose skipping, possible changes in symptoms and/or drug use after skipping a dose for the patients who were diagnosed with bee or vespid venom allergy, allergic rhinitis (AR) and/or allergic asthma receiving the SCIT at regular intervals. In addition, we aimed to analyze how many of the patients who underwent AIT were diagnosed with concomitant COVID-19 infection, the course of their disease and the possible changes in AIT treatment practices in these patients.

MATERIALS AND METHODS

Study population

This retrospective study included 215 adults who received AIT with aeroallergens and bee or vespid venom due to hymenoptera venom anaphylaxis, AR or allergic asthma between 11

March 2020 and 31 January 2021 at Ankara University Faculty of Medicine, Department of Chest Diseases, Immunology and Allergy Clinic and whose information could be accessed. Venom immunotherapy (VIT) was administered to patients with history of systemic allergic reaction after *Apis mellifera* or *Vespula vulgaris* sting and with a positive skin prick test (SPT)/intradermal test and/or positive specific immunoglobulin E (sIgE) diagnostic tests for the culprit insect venom. In patients with moderate-to-severe AR, AIT was applied in addition to avoidance measures and medical treatment to individuals in whom the clinically responsible allergen was detected by history, SPT and high sIgE levels. In addition, AIT was administered to patients with allergic mild to moderate asthma accompanied by AR.

The diagnosis and treatment of AR and asthma were in accordance with ARIA and The Global Initiative for Asthma (GINA) guidelines [7, 8]. The diagnosis and treatment of venom allergy was determined according to the EAACI guidelines [9].

The data used in this study were collected from the medical files including detailed information filled out by physicians at each routine clinical visit. Treatment interruptions, drop-outs and their reasons were asked through telephone interviews with patients.

Administration of AIT

Patients received AIT perennial (year around) or preseasonal. Perennial practice was started with the conventional or cluster method for dose increase period, and maintenance injections were administered to the patients at intervals of monthly or 6 to 8 weeks. In patients receiving VIT, the dose range was extended in accordance with the EAACI guidelines [9]. In the preseasonal administration, 7 injections were made weekly before the pollen season start. While evaluating the compliance with treatment, patients whose AIT was discontinued due to delay in the import of the vaccine or completion of treatment were excluded.

It is suggested that AIT can be continued in any asymptomatic patients without suspicion for SARS-CoV-2 infection and/or contact to positive individuals, in any patient with negative test result or in any patient after an adequate quarantine. It has been stated that AIT can be administered to patients who recover from COVID-19 or who have an adequate SARS-CoV-2 antibody response after asymptomatic disease. Confirmed cases should stop AIT, independent of disease severity until the symptoms have completely resolved [6, 10]. In line with this recommendation, we evaluated our patients in terms of COVID-19 infection, adherence to AIT injections and administered the dose of AIT accordingly, during the pandemic. Furthermore, all patients with respiratory allergy infected with SARS-CoV-2 were asked about disease severity and medication used. The study protocol was approved by the local Ethics Committee of Ankara University, Ankara Turkey (No: I3-183-21).

Statistics analysis

Statistical evaluation of the data obtained was made with SPSS ver. 11.5 (SPSS Inc., Chicago, IL, USA). For categorical variables, frequency (percent) and for metric variables, mean±standard deviation were given as descriptive statistics. In order to compare independent groups in terms of categorical variables, chi-square test, that of metric variables, Student *t* test/Mann-Whitney *U* test were done. A *p* value of <0.05 was considered as statistically significant.

RESULTS

A total of 215 adult patients were included in the study. The mean age was 37.8±11.9 years. One hundred twelve of the patients (112) were female. For AIT, 186 patients came from Ankara. Majority of people were university graduates (54%). Twenty percent (20%) of the patients were active smokers. Considering the body mass index (BMI), 56.3% of the patients were evaluated above normal. The demographic characteristics of the patients are listed in **Table 1**.

Of the patients treated with AIT, 27% had venom allergy, 54.4% had only AR, and 18.6% had asthma accompanied by AR. Immunotherapy protocol was administered to 161 people as perennial and to 54 people as preseasonal. Forty-one point nine percent (41.9%) of the patients undergoing AIT has been received treatment for 3 years or more. The number of subjects who took AIT against venom, pollen, house dust mite, cat and dog dander allergens was 58, 107, 30, 19, 1, respectively. The information of the patients about immunotherapy features is shown in **Table 2**.

Thirty-five point four percent of the patients who received perennial treatment did not continue their treatment due to various reasons after COVID-19 infection. It was their choice not to continue AIT in 66.7% of the patients; the fear of catching COVID-19 during their visit to the hospital throughout the pandemic or public transportation barriers were effective in this decision. AIT was stopped upon completion of the treatment period in 19.3% patients. Three patients could not continue the treatment because they could not provide the vaccine supply. In 3 patients, treatment was interrupted because AIT had to be started from the beginning due to the long-term extending SCIT administration interval. In 2 patients, AIT was not continued with the joint decision of the physician and the patient. The reasons for perennial AIT discontinuation are shown in **Fig. 1**. When the patients who stopped the

Table 1. Demographic characteristics of patients receiving allergen-specific immunotherapy

Characteristic	Value
Age (yr)	37.8±11.9
Sex	
Female	112 (52.1)
Male	103 (47.9)
Place of residence	
Ankara	186 (86.5)
Outside Ankara	29 (13.5)
Education level	
Primary school	18 (8.4)
Middle school	11 (5.1)
High school	36 (16.7)
Associate degree	6 (2.8)
University	116 (54)
Master's degree	27 (12.6)
Doctorate	1 (0.5)
Active smoking	
No	172 (80)
Yes	43 (20)
Body mass index	
Weak	8 (3.7)
Normal	86 (40)
Overweight	87 (40.5)
Obese	33 (15.3)
Morbid	1 (0.5)

Values are presented as mean±standard deviation or number (%).

https://doi.org/10.5415/apallergy.2021.11.e38

Table 2. Immunotherapy information of patients receiving AIT

Variable	Value
AIT indication	
VIT	58 (27)
AR	117 (54)
AR + asthma	40 (18.6)
AIT schedule	
Perennial	161 (74.9)
Preseasonal	54 (25.1)
AIT type of allergen	
Venom	58 (27)
Pollen	107 (49.8)
House dust mite	30 (14)
Cat dander	19 (8.8)
Dog dander	1 (0.5)
AIT duration (yr)	
<3	125 (58.1)
≥3 & <5	76 (35.4)
≥5	14 (6.5)

Values are presented as number (%).
AIT, allergen-specific immunotherapy; VIT, venom immunotherapy; AR, allergic rhinitis.

treatment due to the completion of the treatment and delay in the import of the vaccine were excluded, the rate of patients who compliance the treatment was 70.7%. In addition, 4 patients started SCIT during the pandemic, 2 of them received it for hymenoptera venom and the other 2 for house dust mite.

Among 161 patients, the distribution of venom, pollen, house dust mite, cat, and dog allergens used for perennial AIT was in 58, 53, 30, 19, and 1 subject, respectively. If we examined the rates of continuation of vaccine in terms of allergens in patients using perennial AIT; we found 77.6% for venom, 58.5% for pollen, 46.7% for house dust mite, 73.7% for cats, and 0% for a dog allergen. With regard to the compliance rates to AIT, the percentages were 86.5%, 66%, 50%, 73.7%, 0% for venom, pollen, house dust mite, cat, and dog dander, respectively. Compliance in perennial AIT is shown in **Table 3**. Among the ones receiving perennial AIT, the compliance rate was 64.6% in the group giving treatment for less than 3 years, and 78.5% in those patients for 3 years or more.

During the maintenance phase, distribution of interval rates of injections were 57.1% in 4 weeks, 33.5% in 6 weeks, and 9.3% in 8 weeks, respectively. Out of 104 patients who received perennial AIT and continued treatment, 3 patients did not skip their doses. In the skipped group (97.1%), a minimum of one dose and a maximum of 5 doses were missed.

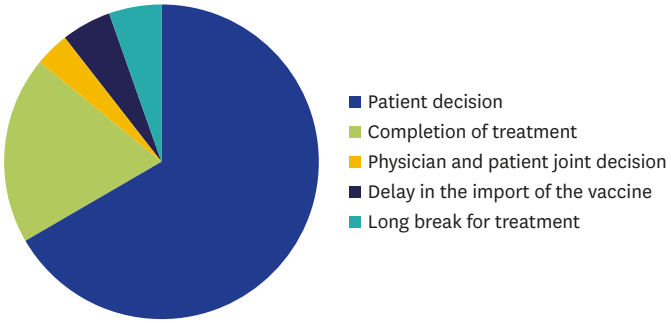

Fig. 1. Reasons for discontinuation of perennial allergen-specific immunotherapy.

https://doi.org/10.5415/apallergy.2021.11.e38

Table 3. The rates of compliance according to types of allergens in patients treated with perennial AIT

Allergen	Total	Continue treatment	Compliance (%)
Venom	58 (36)	45/58 (77.6)	86.5
Pollen	53 (32.9)	31/53 (58.5)	66
House dust	30 (18.6)	14/30 (46.7)	50
Cat	19 (11.8)	14/19 (73.7)	73.7
Dog	1 (0.6)	0/1 (0)	0

Values are presented as number (%).
AIT, allergen-specific immunotherapy.

At least one dose of AIT was missed in 59 people in the group receiving treatment for AR or asthma accompanied by AR. After the dose skipping, 55.9% of these patients did not have an increase in their disease-related symptoms. The percentages of patients reported increase in symptoms of rhinitis, conjunctivitis, and asthma were 39%, 15.3%, and 10.2%, respectively. Furthermore, 40.7% of this group required additional symptomatic medication.

The start of the pollen season coincided with COVID-19 outbreak peak. Therefore, in our clinical practice, sublingual immunotherapy (SLIT) was recommended to patients who received preseasonal SCIT in order to reduce patient contact and hospital admissions. However, the health insurance system does not pay for SLIT vaccine. Thus, 43 out of 54 patients who received preseasonal SCIT discontinued treatment. Nine patients switched to SLIT with their preference in line with our recommendations. Remaining 2 patients reported that they continued SCIT at a different center.

Thirty-four patients (15.8%) were diagnosed with COVID-19 infection. The mean age of patients was 38.5±11.9 years and 58.8% were male. Among these patients, 17.6% had hypertension, 14.7% had asthma, 11.8% had diabetes, and 5.9% had atherosclerotic cardiovascular disease. In addition, 5.9% of these patients used inhaled corticosteroid (ICS), but did not use angiotensin converting enzyme inhibitor (ACEI). Among patients; 16.8% of those who received perennial AIT and 13% of those who received preseasonal treatment were infected with COVID-19 virus. Thirteen patients (38.2%) belong to the VIT group. Four subjects were diagnosed with COVID-19 in isolation at home, while 30 people were diagnosed during a hospital visit. Thirty patients (88.2%) were diagnosed by polymerase chain reaction (PCR), 3 patients (8.8%) by PCR and computed tomography, and 1 patient (2.9%) by clinical findings. Twenty-six of the diagnosed people (76.5%) had reported domestic contacts. Three people were asymptomatic, 29 people were symptomatic, and the information of 2 people was not available. Three patients did not receive any treatment for COVID-19, and information about the treatment of 2 people could not be obtained. Thirty-one patients (91.2%) were home-cured and 3 patients (8.8%) received their treatment in the hospital. The patients treated in the hospital did not need intensive care unit or mechanical ventilator. No drug-related hypersensitivity reaction was observed in patients diagnosed with COVID-19 and also receiving treatment. The information of patients diagnosed with COVID-19 is seen in **Table 4**.

Eighteen out of 34 patients having COVID-19 infection stopped SCIT whereas the remaining patients continued AIT after recovering. Among them, 75% patients showed disruption or delay in SCIT injections. No statistically significant difference was found between patients with and without a diagnosis of COVID-19 infection when they are compared in terms of age, sex, smoking, BMI, education level, ACEI use, ICS use and inhalant or other allergen sensitivity. When these 2 groups were compared in terms of AIT duration, schedule, venom, or inhalant allergy, no significant difference was observed.

https://doi.org/10.5415/apallergy.2021.11.e38

Table 4. Characteristics of patients diagnosed with COVID-19

Characteristic	Value
Age (yr)	38.5±11.9
Sex	
Female	14 (41.2)
Male	20 (58.8)
Comorbidity	
Diabetes	4 (11.8)
Hypertension	6 (17.6)
ASCVD	2 (5.9)
Asthma	5 (14.7)
Drug	
ACEI	0 (0)
ICS	2 (5.9)
COVID-19 diagnosis site	
Home	4 (11.8)
Hospital	30 (88.2)
COVID-19 diagnostic method	
PCR	30 (88.2)
PCR+CT	3 (8.8)
Clinical data	1 (2.9)
COVID-19 domestic contact	
No	8 (23.5)
Yes	26 (76.5)
COVID-19 symptom	
Asymptomatic	3 (8.8)
Symptomatic	29 (85.3)
N/A	2 (5.9)
COVID-19 treatment	
Not received	3 (8.8)
Has taken	29 (85.3)
N/A	2 (5.9)
COVID-19 follow-up	
Home	31 (91.2)
Hospital	3 (8.8)

Values are presented as mean±standard deviation or number (%).
COVID-19, coronavirus disease 2019; ASCVD, atherosclerotic cardiovascular disease; ACEI, angiotensin converting enzyme inhibitor; ICS, ınhaled corticosteroid; PCR, polymerase chain reaction; CT, computed tomography; N/A, not available.

DISCUSSION

Here, we present the general attitudes with regard to their compliance to regular clinical visits of 215 patients followed in our clinic who currently underwent subcutaneous AIT, new patients that we started AIT during the COVID-19 pandemic, as well as the diagnosis and course of COVID-19 infection of all patients who administered AIT.

AIT has the ability to induce long-term tolerance if it can be regularly administrated as both subcutaneous and sublingual route [1, 11]. After the unexpected emergence of the COVID-19 pandemic, many abrupt adjustments for allergy and immunology practices in the clinics including telemedicine, reduction in face to face interviews and open offices has been established in countries. According to international guidelines, schedule modification could be considered in patients receiving inhalant allergen immunotherapy to prevent stopping during the COVID-19 pandemic. It is not necessary to discontinue AIT, especially VIT. VIT should be started or continued for patients having anaphylaxis. While it is suggested that in SCIT, time interval between successive doses can be prolonged depending on the

characteristics of the allergen product used in the treatment; for SLIT, it is recommended to have enough tablets for the possible quarantine period [10, 12].

In a study conducted with pediatric patients in Turkey, the rate of discontinuation of SCIT treatment during the pandemic period was 28.7% [13]. Again, in another study performed in children, the rate of cessation of treatment was 20.5%, and patients' fear of transmission of COVID-19 virus was reported as the primary reasons [14]. In a study from China in the prepandemic period, the rate of continuation of treatment in children and adults was 64.6%, while it was 55% only in adults. In addition, when evaluated in terms of continuation of treatment, families of children population were found to be more adherent [15]. In our study, 35.4% of the patients who received perennial treatment did not continue the treatment. Excluding the patients who stopped the AIT due to completion or lack of vaccine product, compliance rate was 70.7%. This rate can be considered as high for adult patients, especially during the pandemic. Moreover, pandemic has not only resulted in the discontinuation of AIT, but also caused the doses not to be administered on time. Ninety-seven point one percent of patients who continued perennial therapy experienced a dose skipping at least once.

Ozturk et al. [16] reported the study based on 20-item questionnaire data in which only 31% of the respondents (allergy/immunology physicians) discontinued SCIT if the AIT was in the up-dosing phase as well as 72% of responders prolonged injection intervals at 6 weeks during maintenance. In an adult study by Yeğit et al. [17], adherence to SCIT with aeroallergens was investigated according to the delays in SCIT dosing intervals during the COVID-19 pandemic. In accordance with our study, they found that 31.8% patients were considered as nonadherent which most of them was received SCIT with house dust mite allergen and using public transportation for reaching the hospital. In their study, delay in AIT injections led to a deterioration in clinical symptomatology.

In the retrospective study as an EAACI survey from different countries by Pfaar et al. [18], it was reported all information available regarding tolerability and possible changes in daily practice of SLIT and SCIT for inhalant allergies and venom AIT. Of the 417 respondents providing AIT to their patients, 60% informed of not having started SCIT, 40% venom, and 35% SLIT for patients without COVID-19 infection or any suspicion. However, SCIT was continued by 75% of respondents, 74% venom AIT, and 89% SLIT AIT during the maintenance phase as similar rate with our compliance data. The authors commented that AIT not initiated in most of the cases may poorly affect on the clinical care of allergic patients in long term.

As seen, similar nonadherence rates were detected in adult patients giving SCIT in Turkey during the COVID-19 outbreak. In accordance with other studies, for our patients using public transportation as an inconvenience of travel during pandemic was the main reason of premature stop of SCIT injection visits in order to reduce the risk of being infected. From this point of view, administrating SLIT at home seems to be a rational approach for the appropriate patient group during the pandemic.

In a study conducted in Italy, 9.6% of 292 patients who received VIT during the pandemic were discontinued [19]. In Spain, 6.5% of patients who underwent VIT refused to receive treatment due to fear of coronavirus transmission and decided not to continue treatment [20]. In our study, patients who received VIT constituted the group that continued AIT at the highest rate, and 13.5% of those patients were noncompliant. The fact that VIT mainly targets life-threatening allergen can be considered to positively affect the compliance of treatment.

https://doi.org/10.5415/apallergy.2021.11.e38

In contrast to other studies, in which long treatment duration was found to be associated with poor adherence [21], when we analyze with respect to the duration of SCIT; among the ones who received perennial therapy, the rate of compliance was higher in people with a treatment duration of more than 3 years versus less than 3 years. We can speculate that this adherence may be related to the improvement of clinical conditions of these patients with long-term AIT. Not continuing the treatment was the own decision of patients in 66.1% of the cases. As the reasons, uneasiness about applying to the hospital due to the fear of being COVID-19, and transportation problems were stated. For SCIT, an optimal target monthly maintenance dose has to be administered for effectiveness. As an important issue, the extended spacing interval of injections may result in a diminution of therapeutic efficacy. Thus, as soon as the risk for SARS-CoV-2 transmission and infection can be reduced to levels considered safe by health authorities, to make appropriate dose adjustments to restart SCIT and to return to the maintenance AIT schedule known to be effective has been suggested after gaps in the administration [22]. In 97.1% of our patients, SCIT injections were interrupted at least one dose and maximum 5 doses. However, acceptable percent of these patients (55.9%) did not have any deterioration related to diseases after dose skipping. Unfortunately, we observed that 40.7% of patients reported in increase in mainly nasal symptoms required additional use of medication.

The lack of published clinical studies on the outcome of COVID-19 in allergic patients under AIT causes the information to remain theoretical [23]. Our study presents a real-life data that will contribute to theoretical knowledge. The diagnosis rate of COVID-19 was recorded as 15.8% in patients who underwent AIT in our study. Although it was not statistically significant in patients diagnosed with COVID-19, there was a male predominance. Of the patients with COVID-19 diagnosis, 13 patients (38.2%) belong to the VIT group. In a study by Dell'Edera et al. [24], the frequency and severity of COVID-19 infection were investigated in 211 patients receiving VIT. They found only one patient in the overall group who had a mild course of symptoms associated with COVID-19 and 25% of patients had a confirmed contact with a positive subject. This low prevalence was tried to explained with the immune tolerance inducing mechanisms during VIT.

Ninety-one point two percent of the COVID-19 diagnosed patients were home-cured, the remaining patients received hospital-treatment, but none of the patients needed intensive care or mechanical ventilator. Although hypertension, diabetes, chronic obstructive pulmonary disease, heart diseases, malignancies, and human immunodeficiency virus are known as risk factors for life-threatening COVID-19, there is no proven information for asthma, AR or other allergic diseases [25]. No need for intensive care and mechanical ventilator supports the idea that allergic diseases are not a risk factor for severe COVID-19. The overall pooled mortality rate of COVID-19 was found to be 1.53%, out of cases reported by 216 countries [26]. Fortunately, no mortality was observed in our patients. However, we did not find any risk factor for COVID-19 in patients receiving AIT. In the current study, we presented our findings regarding the management of AIT practice, behaviors of physicians and patients during the pandemic. Of course, social restrictions and lockdown requirements to prevent transmission COVID-19 infection may affect daily life and mental state. In this regard, limited data are available about the effect of AIT on COVID-19 infection.

In conclusion, this study showed that COVID-19 has reduced compliance to AIT. During the COVID-19 period, the rate of compliance was 70.7%. The most important factor seems to be fear of patients coming to the hospital visits and transportation problems. Compliance

is higher in VIT targeting life-threatening allergen. In addition, in the majority of patients in perennial SCIT group, at least one dose of injection was missed during pandemic. In patients who underwent AIT, the clinical course of COVID-19 was not severe and no death was observed.

ACKNOWLEDGEMENTS

We thank nurses Emel Eymirli and Yelda Ateş for technical support.

REFERENCES

1. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, Ryan D, Agache I, Ansotegui IJ, Arasi S, Du Toit G, Fernandez-Rivas M, Geerth van Wijk R, Jutel M, Kleine-Tebbe J, Lau S, Matricardi PM, Pajno GB, Papadopoulos NG, Penagos M, Santos AF, Sturm GJ, Timmermans F, van Ree R, Varga EM, Wahn U, Kristiansen M, Dhami S, Sheikh A, Muraro A. EAACI guidelines on allergen immunotherapy: prevention of allergy. Pediatr Allergy Immunol 2017;28:728-45.
PUBMED | CROSSREF
2. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, Halken S, Larenas-Linnemann D, Pawankar R, Pitsios C, Sheikh A, Worm M, Arasi S, Calderon MA, Cingi C, Dhami S, Fauquert JL, Hamelmann E, Hellings P, Jacobsen L, Knol EF, Lin SY, Maggina P, Mösges R, Oude Elberink JNG, Pajno GB, Pastorello EA, Penagos M, Rotiroti G, Schmidt-Weber CB, Timmermans F, Tsilochristou O, Varga EM, Wilkinson JN, Williams A, Zhang L, Agache I, Angier E, Fernandez-Rivas M, Jutel M, Lau S, van Ree R, Ryan D, Sturm GJ, Muraro A. EAACI guidelines on allergen ımmunotherapy: allergic rhinoconjunctivitis. Allergy 2018;73:765-98.
PUBMED | CROSSREF
3. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early transmission dynamics in Wuhan, China, of novel coronavirus-ınfected pneumonia. N Engl J Med 2020;382:1199-207.
PUBMED | CROSSREF
4. World Health Organization (WHO) [Internet]. Geneva (Switzerland): World Health Organization. Coronavirus disease 2019 (COVID-19) situation report – 51 [cited 2021 Jun 27]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10
5. Izquierdo-Domínguez A, Rojas-Lechuga MJ, Alobid I. Management of allergic diseases during COVID-19 outbreak. Curr Allergy Asthma Rep 2021;21:8.
PUBMED | CROSSREF
6. Klimek L, Jutel M, Akdis C, Bousquet J, Akdis M, Bachert C, Agache I, Ansotegui I, Bedbrook A, Bosnic-Anticevich S, Canonica GW, Chivato T, Cruz AA, Czarlewski W, Del Giacco S, Du H, Fonseca JA, Gao Y, Haahtela T, Hoffmann-Sommergruber K, Ivancevich JC, Khaltaev N, Knol EF, Kuna P, Larenas-Linnemann D, Melen E, Mullol J, Naclerio R, Ohta K, Okamoto Y, O'Mahony L, Onorato GL, Papadopoulos NG, Pawankar R, Pfaar O, Samolinski B, Schwarze J, Toppila-Salmi S, Shamji MH, Teresa Ventura M, Valiulis A, Yorgancioglu A, Matricardi P, Zuberbier TARIA-MASK Study Group. Handling of allergen immunotherapy in the COVID-19 pandemic: an ARIA-EAACI statement. Allergy 2020;75:1546-54.
PUBMED | CROSSREF
7. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, Brignardello-Petersen R, Canonica GW, Casale T, Chavannes NH, Correia de Sousa J, Cruz AA, Cuello-Garcia CA, Demoly P, Dykewicz M, Etxeandia-Ikobaltzeta I, Florez ID, Fokkens W, Fonseca J, Hellings PW, Klimek L, Kowalski S, Kuna P, Laisaar KT, Larenas-Linnemann DE, Lødrup Carlsen KC, Manning PJ, Meltzer E, Mullol J, Muraro A, O'Hehir R, Ohta K, Panzner P, Papadopoulos N, Park HS, Passalacqua G, Pawankar R, Price D, Riva JJ, Roldán Y, Ryan D, Sadeghirad B, Samolinski B, Schmid-Grendelmeier P, Sheikh A, Togias A, Valero A, Valiulis A, Valovirta E, Ventresca M, Wallace D, Waserman S, Wickman M, Wiercioch W, Yepes-Nuñez JJ, Zhang L, Zhang Y, Zidarn M, Zuberbier T, Schünemann HJ. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol 2017;140:950-8.
PUBMED | CROSSREF

8. Mauer Y, Taliercio RM. Managing adult asthma: The 2019 GINA guidelines. Cleve Clin J Med 2020;87:569-75.
PUBMED | CROSSREF

9. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilò MB, Akdis CA, Antolín-Amérigo D, Cichocka-Jarosz E, Gawlik R, Jakob T, Kosnik M, Lange J, Mingomataj E, Mitsias DI, Ollert M, Oude Elberink JNG, Pfaar O, Pitsios C, Pravettoni V, Ruëff F, Sin BA, Agache I, Angier E, Arasi S, Calderón MA, Fernandez-Rivas M, Halken S, Jutel M, Lau S, Pajno GB, van Ree R, Ryan D, Spranger O, van Wijk RG, Dhami S, Zaman H, Sheikh A, Muraro A. EAACI guidelines on allergen immunotherapy: hymenoptera venom allergy. Allergy 2018;73:744-64.
PUBMED | CROSSREF

10. Klimek L, Pfaar O, Worm M, Bergmann KC, Bieber T, Buhl R, Buters J, Darsow U, Keil T, Kleine-Tebbe J, Lau S, Maurer M, Merk H, Mösges R, Saloga J, Staubach P, Stute P, Rabe K, Rabe U, Vogelmeier C, Biedermann T, Jung K, Schlenter W, Ring J, Chaker A, Wehrmann W, Becker S, Mülleneisen N, Nemat K, Czech W, Wrede H, Brehler R, Fuchs T, Tomazic PV, Aberer W, Fink-Wagner A, Horak F, Wöhrl S, Niederberger-Leppin V, Pali-Schöll I, Pohl W, Roller-Wirnsberger R, Spranger O, Valenta R, Akdis M, Akdis C, Hoffmann-Sommergruber K, Jutel M, Matricardi P, Spertin F, Khaltaev N, Michel JP, Nicod L, Schmid-Grendelmeier P, Hamelmann E, Jakob T, Werfel T, Wagenmann M, Taube C, Gerstlauer M, Vogelberg C, Bousquet J, Zuberbier T. Allergen immunotherapy in the current COVID-19 pandemic: A position paper of AeDA, ARIA, EAACI, DGAKI and GPA: Position paper of the German ARIA Group[A] in cooperation with the Austrian ARIA Group[B], the Swiss ARIA Group[C], German Society for Applied Allergology (AEDA)[D], German Society for Allergology and Clinical Immunology (DGAKI)[E], Society for Pediatric Allergology (GPA)[F] in cooperation with AG Clinical Immunology, Allergology and Environmental Medicine of the DGHNO-KHC[G] and the European Academy of Allergy and Clinical Immunology (EAACI)[H]. Allergol Select 2020;4:44-52.
PUBMED | CROSSREF

11. Durham SR, Leung DY. One hundred years of allergen immunotherapy: time to ring the changes. J Allergy Clin Immunol 2011;127:3-7.
PUBMED | CROSSREF

12. Shaker MS, Oppenheimer J, Grayson M, Stukus D, Hartog N, Hsieh EWY, Rider N, Dutmer CM, Vander Leek TK, Kim H, Chan ES, Mack D, Ellis AK, Lang D, Lieberman J, Fleischer D, Golden DBK, Wallace D, Portnoy J, Mosnaim G, Greenhawt M. COVID-19: pandemic contingency planning for the allergy and ımmunology clinic. J Allergy Clin Immunol Pract 2020;8:1477-88.e5.
PUBMED | CROSSREF

13. Aytekin ES, Soyer Ö, Şekerel BE, Şahiner ÜM. Subcutaneous allergen ımmunotherapy in children: real life compliance and effect of COVID-19 pandemic on compliance. Int Arch Allergy Immunol 2021;182:631-6.
PUBMED | CROSSREF

14. Kulhas Celik I, Metbulut AP, Uneri OS, Senses Dinc G, Dibek Misirlioglu E. Effect of patient and parental anxiety on adherence to subcutaneous allergen immunotherapy during the coronavirus disease 2019 pandemic. Ann Allergy Asthma Immunol 2021;126:595-7.
PUBMED | CROSSREF

15. Yang Y, Wang Y, Yang L, Wang J, Huang N, Wang X, Hu L, Jiang Q, Liu G, Zhu R. Risk factors and strategies in nonadherence with subcutaneous immunotherapy: a real-life study. Int Forum Allergy Rhinol 2018;8:1267-73.
PUBMED | CROSSREF

16. Ozturk AB, Baççıoğlu A, Soyer O, Civelek E, Şekerel BE, Bavbek S. Change in allergy practice during the COVID-19 pandemic. Int Arch Allergy Immunol 2021;182:49-52.
PUBMED | CROSSREF

17. Yeğit OO, Demir S, Ünal D, Olgaç M, Terzioğlu K, Eyice Karabacak D, Tüzer C, Ayhan V, Çolakoğlu B, Büyüköztürk S, Gelincik A. Adherence to subcutaneous immunotherapy with aeroallergens in real-life practice during the COVID-19 pandemic. Allergy 2022;77:197-206.
PUBMED | CROSSREF

18. Pfaar O, Agache I, Bonini M, Brough HA, Chivato T, Del Giacco SR, Gawlik R, Gelincik A, Hoffmann-Sommergruber K, Jutel M, Klimek L, Knol EF, Lauerma A, Ollert M, O'Mahony L, Mortz CG, Palomares O, Riggioni C, Schwarze J, Skypala I, Torres MJ, Untersmayr E, Walusiak-Skorupa J, Chaker A, Giovannini M, Heffler E, Jensen-Jarolim E, Quecchia C, Sandoval-Ruballos M, Sahiner U, Tomić Spirić V, Alvaro-Lozano M. COVID-19 pandemic and allergen immunotherapy-an EAACI survey. Allergy 2021;76:3504-16.
PUBMED | CROSSREF

19. Bilò MB, Braschi MC, Piga MA, Antonicelli L, Martini M. Safety and adherence to venom ımmunotherapy during COVID-19 pandemic. J Allergy Clin Immunol Pract 2021;9:702-8.
PUBMED | CROSSREF

20. Martínez-Lourido E, Otero A, Armisén M, Vidal C. Comment on: Bilò MB, Pravettoni V, Mauro M, Bonadonna P. Treating venom allergy during COVID-19 pandemic: Management of venom allergen

immunotherapy during the COVID-19 outbreak in Spain. Allergy 2021;76:951-2.
PUBMED | CROSSREF

21. Reisacher WR, Visaya JM. Patient adherence to allergy immunotherapy. Curr Opin Otolaryngol Head Neck Surg 2013;21:256-62.
PUBMED | CROSSREF

22. Larenas-Linnemann DE, Epstein T, Ponda P, Bernstein D, Williams P, Creticos P. Gaps in allergen immunotherapy administration and subcutaneous allergen immunotherapy dose adjustment schedules: Need for prospective data. Ann Allergy Asthma Immunol 2020;125:505-6.e2.
PUBMED | CROSSREF

23. Larenas-Linnemann DE, Ortega-Martell JA, Blandón-Vijil MV, Rodríguez-Pérez N, Luna-Pech JA, Estrada-Cardona A, Arias-Cruz A, Del Rio-Navarro BE, Rodríguez EMN, Pozo-Beltrán CF, Takane EO, Rojo-Gutiérrez MI, Espinosa-Rosales FJ, Martínez-Infante EA. Coronavirus disease 2019, allergic diseases, and allergen immunotherapy: possible favorable mechanisms of interaction. Allergy Asthma Proc 2021;42:187-97.
PUBMED | CROSSREF

24. Dell'Edera A, Borghesan F, Favero E, Rattazzi M, Scarpa R, Tartaglia L, Agostini C, Cinetto F. Venom immunotherapy during COVID-19 pandemic: experience from a University Allergy Center in Northern Italy. World Allergy Organ J 2020;13:100489.
PUBMED | CROSSREF

25. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, Abosalif KOA, Ahmed Z, Younas S. COVID-19 and comorbidities: deleterious impact on infected patients. J Infect Public Health 2020;13:1833-9.
PUBMED | CROSSREF

26. Phannajit J, Takkavatakarn K, Katavetin P, Asawavichienjinda T, Tungsanga K, Praditpornsilpa K, Eiam-Ong S, Susantitaphong P. Factors associated with the incidence and mortality of coronavirus disease 2019 (COVID-19) after 126-million cases: a meta-analysis. J Epidemiol Glob Health 2021;11:289-95.
PUBMED | CROSSREF